

THE EFFECT OF PLANT PHOSPHATIDYL SERINE ON AGE-ASSOCIATED MEMORY IMPAIRMENT AND MOOD IN THE FUNCTIONING ELDERLY

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ABSTRACT

This double-blind study assessed the influence of plant phosphatidylserine (PS) product on memory and mood in functioning elderly, aged 60-80 years old, and living in the community. Seventy-two subjects, randomly assigned to placebo and therapy groups, were treated for three months with 300 mg, PS daily. Results showed a large and statistically significant positive influence of treatment on both memory and mood, whereas influence of placebo was small and non-significant. This influence was stronger with higher pretreatment memory scores. Components of memory and cognition that were most improved by the treatment included memorizing information, visual memory, and memorizing numbers. Mood was also influenced. Winter mood changes ("Winter Blues") did develop in the placebo group but were entirely blocked in those treated with plant PS.

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BACKGROUND

Memory loss that is associated with increasing age (1-3) is distressing to both the aged individual and his family. The clinician must distinguish between two different entities (4). The first is age-associated memory impairment (AAMI) that affects the whole elderly population, where ability to perform demanding everyday memory tasks may decline by 50% or more over adulthood and aging. AAMI is a gradual, "normal" loss of memory (1, 5). The second is memory loss due to Alzheimer's Disease (AD) and other dementing disorders, most of which are irreversible conditions of various kinds that affect a smaller proportion of the aged. The distress associated with these memory impairments has ignited a search for various treatments. Cognitive deficits associated with age have been found to be related to changes in cholinergic, noradrenergic and serotonergic function (6-12), association between age and memory problems has been observed in all mammalian species studied to date, and pharmacological intervention has been repeatedly claimed to rectify such deficits (13-17).

PHOSPHATIDYL SERINE (PS)

Many age-related neurochemical changes can be traced to structural and functional alterations in neuronal membranes(18), which have been related to changes in lipid composition or content in the aging brain (19). This has led to the proposal that administration of endogenously occurring phospholipids may prevent or reverse age-related neurochemical deficits (20).

Phosphatidylserine is a negatively charged phospholipid which is almost exclusively located in cell membranes. PS has a series of unique physiological properties which are implicated in neuronal functions. These include stimulation of neurotransmitter release, activation of ion transport and increase in glucose and cyclic AMP levels in the brain. In aging, decline in these functions is associated with memory impairment and deficits in mental cognitive abilities. In clinical trials results reported by Villardita et.al. (21), AAMI was treated by three-month administration of bovine PS, 300 mg daily, in subjects who reported intellectual deterioration. Few could be described as demented. In his study, improvement occurred in those receiving bovine PS relative to those who received the placebo on a number of neuropsychological tests within an extensive battery.

Crook et al. (1) treated 149 patients meeting criteria for AAMI for 12 weeks with a formulation of phosphatidylserine (100mg BC-PS tid) or placebo. Patients treated with the drug improved relative to those treated with placebo in performance tests related to learning and memory tasks of daily life. Analysis of clinical subgroups suggested that persons who performed at a relatively low level prior to treatment, were most likely to respond to BC-PS. Within this subgroup, there was improvement on both computerized and standard neuropsychological performance test, and also on clinical global ratings of improvement.

The hesitation because of the suspected risk of slow virus infection, prevented health administrations from approving bovine brain PS and stimulated a search for an alternative plant source. In this study we have examined a novel PS product made by enzymatic conversion of soy lecithin. It was assumed that the therapeutic potential of plant PS is identical to that of bovine PS and therefore a dosage of 3 x 100 mg. Per day was chosen (1,5).

METHODS

The study assessed the effect of plant PS on memory performance among elderly residents of Israeli rural collective communities (kibbutzim). Subjects were recruited from among members of three kibbutzim; Givat brenner, Gat, and Galon, in the southern-central region of Israel. Recruitment was accomplished in coordination with the kibbutz health committees and clinics. In order to inform the population of the study and to gain access to them, the nature of the study was explained to the elderly who attended special meetings following articles published in each kibbutz newspaper. Out of a total of 414 kibbutz members aged 60-80, these recruitment efforts resulted in a total of 102 (24.6%) volunteers who reported some memory difficulties.

After invoking the inclusion/exclusion criteria, a total of 72 subjects remained in the study. These criteria, intended to rule out those suffering from conditions that could influence memory, were:

- * Hebrew-speaking men and women aged 60-80 at the time of recruitment.
- * Reported some memory problems in daily life.
- * A score of at least 25 out of 30 on the Folstein Mini Mental State Test (22) (i.e. non-demented)
- * A score of <17 on the List of Depressive Symptoms (23), indicating that the subject was not depressed.
- * Not suffering from any active or recent major disease.
- * Not taking medication that influence memory (sedatives, tranquilizers etc.).

BASELINE MEASURES

Baseline measures included demographic, social, functioning, and health data. Health variables included diseases and medication use. Education was obtained as a continuous

variable of total number of years of education.

DATA ANALYSIS

Data analysis was done using the SPSS-PC statistical package. All p-values are two-tailed unless otherwise indicated. The influence of the main variables was also estimated by the Person chi-square test for categorical data. To estimate the joint effect of the variables we performed both step wise linear regression and multiple linear regression.

OUTCOME MEASURES

All those selected for the study were administered a battery of tests at baseline.

These included:

The Wechsler Memory test (24) which examines memory, learning, association, and information gathering as distinct from intelligence (25). The components of the test are orientation, information, concentration (counting backwards 20-1), saying alphabet backwards, adding by threes to 40, repeating short stories, repeating numbers forward and backward, learning word associations, and visual memory. Because these components measure slightly different abilities, the outcomes were also analyzed in terms of these components. Since we compared two relatively homogeneous groups we did not apply the correction for age that is usually done for the Wechsler Memory Test among young people and adults.

Mood was tested by using the List of Depressive Symptoms (23), a list of 22 items expressing negative affect and 12 items with positive affect. Recording produces a total score. This score was also used as an excluding screening device, and only those with a score of <17 were included in the sample. Conclusions can be drawn as to the mood of the non-depressed.

PHOSPHATIDYL SERINE AND PLACEBO ADMINISTRATION

Participants were randomly assigned to a drug or placebo group, and were administered either a 100 mg, dose of phosphatidylserine mixed with lecithin tid (L-Telect 100 mg. Capsules) or a 500 mg. Dose of lecithin (placebo) tid daily for three months.

FOLLOWUP

At the end of three months, a total of 57 participants were located and administered a second battery of tests. Fifteen subjects were either not located or dropped out of the study for a variety of reasons (e.g. death, non-compliance, surgery).

Analysis of the baseline scores on a variety of measures shows that there were no statistically significant differences between the dropouts and the study group in any dimension examined (Table 1). Proportionally more men than women dropped out and the dropouts tended to have lower baseline Wechsler score, nevertheless, the differences were not significant.

The characteristics of the placebo and drug groups are shown in (Table 2). the percent of females was higher in the drug group than in the placebo group. Also, there were fewer-subjects with three or more diseases than in the placebo group, but again the differences were not significant.

RESULTS

The outcome variables were change in score on the Wechsler Memory Test (WMT)(24) and change in score on

the List of Depressive Symptoms (LDS)(23).

The major outcome measure was the change in WMT score between the baseline (T1) and the follow-up (T2). Figure 1 shows that there was a significant test-retest improvement in total Wechsler scores for both the drug and placebo groups. The changes were significant in both placebo ($p<0.01$) and drug ($p<0.005$) groups, but was larger and more significant in the treatment group.

Further analysis shows that pretreatment, T1 Wechsler Score(Fig.2), had a significant effect on the change in the Wechsler score (Fig. 2). For those with a low (<69) initial score, there was no significant difference at T2 between the placebo group and the drug group ($p<0.91$). However, for those with a higher initial T1 Wechsler score (>68), those who received a placebo actually experienced a small decrease in the T2 Wechsler score, whereas those who received phosphatidylserine experienced a significant increase in T2 Wechsler score that leads to significant differences among groups ($p<0.03$).

Analysis of the nine components that constitute the Wechsler score (Table 3) indicates that there were differential changes in the component scores between the placebo and drug groups. In the placebo group, a change in the WMT test score was found in the total score only (1.73 points increase, $p<0.03$). However, in the drug group, there was a highly significant change in the total score (2.32 points increase, $p<0.001$) as well as in the test's components: information component (2.2%, $p<0.04$), visual memory (10.6%, $p<0.01$) and memorizing numbers (7.0%, $p<0.01$). The only negative relationship was found in adding by threes, and it was not significant.

To estimate the importance of treatment with PS we used multiple linear regression of change in Wechsler score on initial Wechsler(T1) along with drug/placebo assignment and the interaction initial Wechsler score and drug/placebo assignment. The results of this linear regression are shown in (table 4). Receiving phosphatidylserine alone increases the change in the T2 Wechsler score by a large and highly significant amount, as does having a high T1 Wechsler score. Including the interaction term Wechsler at T1 by drug group (placebo or drug) reveals a positive and highly significant interaction between having a high T1 Wechsler score and receiving the drug. This is another indication that there is a greater effect of treatment on those with higher T1 Wechsler scores than on those with lower T1 Wechsler scores.

In assessing mood changes after phosphatidylserine administration, score on the LDS was assessed before and after treatment for the placebo and drug groups (Figure 3). The results show that the placebo group experienced a significant increase in depressive symptoms between T1 (which was late summer) and T2 (winter)(p<0.001), whereas the drug group revealed no significant change (p<0.4).

DISCUSSION

This study not only confirms results of previous studies on the positive effect of PS on memory and mood but also encourages the clinician to consider the drug. At present there are barriers on the use of bovine PS in the US, in Israel (The Pharmacists Ordinance, 1986 May 23rd, Chapter 29/3, the Israel Legislation Registry), and in other countries. These restrictions originated from the suspected slow-virus infection risk by bovine brain extraction products and bovine brain PS as well. Though not yet reported, this suspected risk minimized the clinical use of the drug. In Israel, as in several other countries, the import of bovine brain PS requires a special authorization from the Ministry of Health. Our clinical trial is the first to study the new plant PS compound effect on memory and mood in non-demented, non-depressed, functioning elderly, with various degrees of age-associated memory impairment. Mean results of post-treatment memory testing scores in the treatment group were higher and statistically much more significant compared to the placebo group. Furthermore, when pre and post treatment results of components of the memory test were compared, none of the placebo group's results showed statistically significant results, whereas results of maintaining information, visual memory and memorizing numbers improved with statistical significance of p<0.05, memorizing stories improved with p<0.07, and memorizing pairs of words with p<0.09. Though not statistically significant, we also observed some smaller improvement in the placebo group as well. This may be explained as a learning (test-retest) effect. The results also show association between pre-treatment, Wechsler score on the outcomes. Subjects who received the drug and who had scored higher than 68 on the T1 WMT test showed a more significant memory improvements, whereas those who had scored 68 or less did not. This association was pronounced also in a regression analysis of the data. This particular result is not consistent with the results of Crook (1), where the highest memory improvements was found in those performing at the lowest levels prior to treatment. Probable explanation may

be either by the different tests used in the two studies, or by the possibility that some of our lower-scoring participants were early dementing subjects.

In addition to the positive influence on the memory functions, the results revealed an effect of the drug on mood. None of the participants in the trial has been initially depressed since high LDS scores were excluded. Nevertheless, we observed worsening of mood with time in the placebo group which was fully blocked in the treatment group. "Winter Blues" are a common phenomenon in the elderly. Since our study started in late summer and ended in winter, we suggest that plant PS may be effective in prevention or treatment of "Winter Blues" and depression. Maggioni et. al. (17) reported a positive effect of PS on geriatric depression.

We conclude that there is a positive effect of plant PS on memory and mood in the functioning elderly. Extrapolation of this finding to dementing disorders and depression needs further investigation.

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TABLE 1.

COMPARISON OF STUDY GROUP VERSUS DROP-OUTS.

	Study mean	Group s.d.	Drop mean	Outs s.d.	P
Age	71.07	6.54	68.93	6.25	0.26
Education	11.96	3.05	11.93	3.47	0.97
Wechsler	66.26	7.58	62.71	4.91	0.15
	N	%	N	%	
Sex:					
M	19	33	8	53	
F	38	67	7	47	0.15
Treatment:					
Drug	31	54	9	60	0.82
	26	46	6	40	

Placebo						
Total	57		15			

TABLE 2.
CHARACTERISTICS OF STUDY GROUPS.

		PLACEBO		DRUG		P
		mean	s.d.	mean	s.d.	
AGE		70.80	7.00	6.20	12.40	0.26
EDUCATION		11.40	3.10		3.00	0.97
		N	%	N	%	
SEX:	M	11	42	8	26	0.18 0.39
	F	15	88	23	74	
DRUG:	Y	13	50	31	54	
	N	13	50	19	61	
DISEASE:	NO	8	31	12	39	
	1-2	10	39	14	45	
	3+	8	31	5	16	
TOTAL		26		31		

TABLE 3.
CHANGE IN MEAN SCORES.
COMPONENTS OF WECHSLER MEMORY AFTER TREATMENT

VARIABLES	PLACEBO GROUP			DRUG GROUP		
	Means of	Base Levels Δ (%) P		Means of	Base Levels Δ (%) P	
Wechsler Memory Test	66.00	3.3	.03	66.48	3.5	.001
Score at T1	5.96	0	--	5.87	2.2	.04
Information	5.00	0	--	5.00	0	--
Orientation	13.81	4.0	.30	13.16	6.4	.07

		memoraid3					
Memorizing Stories	9.12	9.2	.09	10.06	10.6	.01	
Visual Memory	10.85	2.9	.18	10.61	7.0	.01	
Memorizing Numbers	15.58	1.9	.49	16.03	4.1	.09	
Memor.Pairs of Words	2.15	5.0	.27	2.13	2.9	.49	
Counting Backward	2.15	9.0	.33	1.42	20.4	.14	
Saying the Alphabet	2.62	1.0	.87	2.26	-3.9	.57	
Adding by Threes							

TABLE 4.
MULTIPLE REGRESSION
CHANGES IN WECHSLER MEMORY SCORE

VARIABLES	B	BETA	P
WECHSLER(T1)	-0.33	-0.61	.001
WECHSLER(TREAT)	0.42	3.47	.003
TREATMENT	27.39	3.38	.003

R sq.= .20 P<.009

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